inflammatory effects *in vitro*. Some antipsoriasis drugs, such as cyclosporin A and anthralin, have been shown to inhibit PKC, and inhibition of PKC has been suggested as a therapeutic approach to the treatment of psoriasis (Hegemann, L. and G. Mahrle, *Pharmacology of the Skin*, H. Mukhtar, ed., pp. 357-368, CRC Press, Boca Raton, FL, 1992). Antisense compounds targeted to Protein Kinase C (PKC) proteins are described in U.S. Patents Nos. 5,620,963 to Cook *et al.* and 5,681,747 to Boggs *et al.*

[0101] Another type of therapeutic indication of interest is inflammatory disorders of the skin. These occur in a variety of forms including, for example, lichen planus, toxic epidermal necrolyis (TEN), ertythema multiforme and the like (*The Merck Manual of Diagnosis and Therapy*, 15th Ed., pp. 2286-2292, Berkow *et al.*, eds., Rahway, N.J., 1987). Expression of ICAM-1 has been associated with a variety of inflammatory skin disorders such as allergic contact dermatitis, fixed drug eruption, lichen planus and psoriasis (Ho *et al.*, *J. Am. Acad. Dermatol.*, 1990, *22*, 64; Griffiths *et al.*, *Am. J. Pathology*, 1989, *135*, 1045; Lisby *et al.*, *Br. J. Dermatol.*, 1989, *120*, 479; Shiohara *et al.*, *Arch. Dermatol.*, 1989, *125*, 1371; Regezi *et al.*, *Oral Surg. Oral Med. Oral Pathol.*, 1996, *81*, 682). Moreover, intraperitoneal administration of a monoclonal antibody to ICAM-1 decreases ovalbumin-induced eosinophil infiltration into skin in mice (Hakugawa *et al.*, *J. Dermatol.*, 1997, *24*, 73). Antisense compounds targeted to ICAM-1 are described in U.S. Patents Nos. 5,514,788 and 5,591,623, and co-pending U.S. patent applications Serial Nos. 09/009,490 and 09/062,416, January 20, 1998 and April 17, 1998, respectively, all to Bennett *et al.*

[0102] Other antisense targets for skin inflammatory disorders are VCAM-1 and PECAM-1. Intraperitoneal administration of a monoclonal antibody to VCAM-1 decreases ovalbumin-induced

eosinophil infiltration into the skin of mice (Hakugawa *et al.*, *J. Dermatol.*, 1997, *24*, 73). Antisense compounds targeted to VCAM-1 are described in U.S. Patents Nos. 5,514,788 and 5,591,623. PECAM-1 proteins are glycoproteins which are expressed on the surfaces of a variety of cell types (for reviews, see Newman, *J. Clin. Invest.*, 1997, *99*, 3 and DeLisser *et al.*, *Immunol. Today*, 1994, *15*, 490). In addition to directly participating in cell-cell interactions, PECAM-1 apparently also regulates the activity and/or expression of other molecules involved in cellular interactions (Litwin *et al.*, *J. Cell Biol.*, 1997, *139*, 219) and is thus a key mediator of several cell:cell interactions. Antisense compounds targeted to PECAM-1 are described in co-pending U.S. patent application Serial No. 09/044,506, filed March 19, 1998, by Bennett *et al.*

[0103] Another type of therapeutic indication of interest for oligonucleotides encompasses a variety of cancers of the skin. Representative skin cancers include benign tumors (warts, moles and the like) and malignant tumors such as, for example, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, Kaposi's sarcoma and the like (*The Merci Manual of Diagnosis and Therapy*, 15th Ed., pp. 2301-2310, Berkow *et al.*, eds., Rahway, N.J., 1987). A number of molecular targets involved in tumorigenesis, maintenance of the hyperproliferative state and metastasis are targeted to prevent or inhibit skin cancers, or to prevent their spread to other tissues.

[0104] The *ras* oncogenes are guanine-binding proteins that have been implicated in cancer by, *e.g.*, the fact that activated ras oncogenes have been found in about 30% of human tumors generally; this figure approached 100% in carcinomas of the exocrine pancreas (for a review, see Downward, *Trends in Biol. Sci.*, 1990, *15*, 469). Antisense compounds targeted to H-ras and K-ras are described

in U.S. Patent No. 5,582,972 to Lima *et al.*, 5,582,986 to Monia *et al.* and 5,661,134 to Cook *et al.*, and in published PCT application WO 94/08003.

[0105] Protein Kinase C (PKC) proteins have also been implicated in tumorigenesis. Antisense compounds targeted to Protein Kinase C (PKC) proteins are described in U.S. Patents Nos. 5,620,963 to Cook *et al.* and 5,681,747 to Boggs *et al.* Also of interest are AP-1 subunits and JNK proteins, particularly in regard to their roles in tumorigenesis and metastasis. The process of metastasis involves a sequence of events wherein (1) a cancer cell detaches from its extracellular matrices, (2) the detached cancer cell migrates to another portion of an animal's body, often *via* the circulatory system, and (3) attaches to a distal and inappropriate extracellular matrix, thereby created a focus from which a secondary tumor can arise. Normal cells do not possess the ability to invade or metastasize and/or undergo apoptosis (programmed cell death) if such events occur (Ruoslahti, *Sci. Amer.*, 1996, *275*, 72). However, many human tumors have elevated levels of activity of one or more matrix metalloproteinases (MMPs) (Stetler-Stevenson *et al.*, *Annu. Rev. Cell Biol.*, 1993, *9*, 541; Bernhard *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)*, 1994, *91*, 4293. The MMPs are a family of enzymes which have the ability to degrade components of the extracellular matrix (Birkedal-Hansen, *Current Op. Biol.*, 1995, *7*, 728). In particular, one member of this family, matrix metalloproteinase-9 (MMP-9), is often found to be expressed only in tumors and other diseased tissues (Himelstein *et al.*, *Invasion & Metastasis*, 1994, *14*, 246).

[0106] Several studies have shown that regulation of the MMP-9 gene may be controlled by the AP-1 transcription factor (Kerr *et al.*, *Science*, 1988, *242*, 1242; Kerr *et al.*, *Cell*, 1990, *61*, 267; Gum *et al.*, *J. Biol. Chem.*, 1996, *271*, 10672; Hua *et al.*, *Cancer Res.*, 1996, *56*, 5279). Inhibition of AP-1